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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-363**

Medical Review(s)

CLINICAL REVIEW

Executive Summary Section

NDA 21,363 Clarinet tablets Perennial Allergic Rhinitis

Proprietary name: Clarinet

Established name: desloratadine

Sponsor: Schering

Category of Drug: antihistamine

Review Date: 28 January 2002

Documents Reviewed: Submissions of 9 April 2001 and 7 August 2001

Application Type: original NDA for use of this drug product for treatment of perennial allergic rhinitis

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Clinical Review for NDA 21,363**Executive Summary****I. Recommendations**

- A. Recommendation on Approvability: Clarinex in the tablet formulation has been shown to be efficacious and safe for administration in patients 12 years of age and older at a dose of 5 mg per day for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).**
- B. Recommendation on Phase 4 Studies and/or Risk Management Steps: It was recommended that the sponsor attempt to determine the mechanism accounting for higher levels of drug exposure in some patients, and to assess the potential for drug-drug interactions that might be expected depending on the outcome of these investigations.**

II. Summary of Clinical Findings

- A. Brief Overview of Clinical Program: Under the original NDA (NDA 21,165) the sponsor had submitted 4 studies evaluating the safety and effectiveness of Clarinex for the treatment of SAR. Based on those studies Clarinex was shown to be safe and effective in the treatment of SAR, in patients 12 years of age and older, for which approval was granted. The sponsor has submitted under NDA 21,363, 2 studies assessing the safety and effectiveness of Clarinex for the treatment of PAR and 2 studies evaluating the effectiveness and safety of Clarinex in patients 12 years of age and older, who have concomitant SAR and asthma. Based on the data from these studies, the sponsor has demonstrated the safety and effectiveness of Clarinex for the treatment of PAR and SAR in patients 12 years of age and older.**

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- B. Efficacy:** The sponsor demonstrated the efficacy of Clarinex in the treatment of SAR in NDA 21,165. In this NDA, the sponsor has demonstrated the efficacy of Clarinex in one of two studies for the treatment of PAR. There is no data to indicate conclusively that there is any difference in the underlying pathophysiology of SAR and PAR, nor reason to believe that a specific treatment that is effective for one would not be effective for the other. Therefore, the sponsor has adequately demonstrated the efficacy of Clarinex for both SAR and PAR (also see Section IV).
- C. Safety:** Studies in adult patients have demonstrated that approximately 6% are slow metabolizers, compared with approximately 15% of pediatric patients studied. It has also been shown that 72% of patients who are slow metabolizers are African-American. Approximately 20% of African-Americans are slow metabolizers. The enzyme responsible for the metabolism of desloratadine to 3 OH desloratadine has not been identified. In pooled data, _____) the overall percentage of slow metabolizers who developed adverse events was 21% compared to 31% of patients who were normal metabolizers and 54% of patients who received placebo. Furthermore, the incidence of ECG changes were similar in both slow and normal metabolizers, except that the maximum mean change in ventricular rate from baseline in multiple dose pharmacology studies was 14.63 bpm in slow metabolizers and 5.44 bpm in normal metabolizers, compared to 10.22 bpm in placebo patients. Mean QTc prolongation was 7.3 msec in slow metabolizers, 1.9 msec in normal metabolizers, and 6.5 msec in patients who received placebo. The labeling for Clarinex has been modified to indicate that there is a subset of patients who have a decreased ability to form 3-OH desloratadine who are, therefore, slow metabolizers of desloratadine and that the incidence is greater in African-Americans. The labeling also points out that slow metabolizers can have a 6 fold greater bioavailability than normal metabolizers, that such patients can not be prospectively identified and may be more susceptible to dose-related adverse events (see also Section IV).

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- D. **Dosing:** Clarinex given at a dose of 5 mg once a day is safe and effective in the treatment of SAR and PAR in patients 12 years of age and older.
- E. **Special Populations:** There was no indication that the efficacy or safety of Clarinex was different based on gender, race or age.

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- I. **Introduction and Background:** The sponsor was notified that the NDA for Clarinex (desloratadine) tablets (NDA 21,165) was approvable for the treatment of seasonal allergic rhinitis (SAR) on 19 January 2001. In addition, NDAs have been submitted for: 1) a syrup formulation

a 5 mg tablet for the treatment of chronic urticaria (NDA 21,297), the D-12 extended release _____ tablet of desloratadine

Desloratadine has been approved for marketing as a 5 mg tablet for SAR in 19 countries. The sponsor has now submitted 8 studies in support of the efficacy and safety of desloratadine in the treatment of allergic rhinitis, both PAR and SAR; 4 studies included in the original NDA in patients with SAR (studies 001, 223, 224, 225), 2 studies in patients with PAR (studies 218, 219), and 2 studies in patients with concomitant SAR and asthma (214, 215). NDA 21,363 for Clarinex 5 mg tablets for the treatment of perennial allergic rhinitis (PAR) was submitted by the sponsor on 9 April 2001. The sponsor has shown the efficacy and safety of Clarinex tablets for the treatment of both recognized general categories of allergic rhinitis, SAR and PAR.



Desloratadine is the active metabolite of loratadine (Claritin) which is marketed as a 10 mg tablet in the United States and is a relatively non-sedating H-1 receptor antagonist. When administered orally, loratadine is

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rapidly metabolized to descarboethoxyloratadine (desloratadine), which is the major metabolite of loratadine and is pharmacologically active.

Since loratadine is rapidly metabolized to desloratadine, exposure to desloratadine is greater than exposure to the parent compound. The elimination half-life and AUC for desloratadine are significantly greater than for loratadine.

The inactive ingredients in the desloratadine tablet include dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch and talc. The tablet is coated with  and FDC Blue #2 Lake,  Clear, carnauba wax and white wax. Tablets are supplied in HDPE bottles and in unit dose blisters. The formulation that was used in the study of patients with PAR is the same formulation that was used in the study of patients with SAR, for which the sponsor gained approval under NDA 21,165.

Desloratadine was developed because of improved pharmacokinetic profile over loratadine, based on less extensive first-pass metabolism and a longer plasma elimination half-life. Oral administration of desloratadine results in significant absorption without any food effect. After oral absorption, desloratadine is hydroxylated at the 3 position with subsequent glucuronidation and is excreted to a similar extent in the urine and feces. The long plasma elimination half-life supports once daily dosing.

With increasing awareness of the sedative risks involved with the use of first generation antihistamines, in association with driving or performing mechanical tasks, the importance of second generation relatively non-sedating antihistamines in the management of conditions such as allergic rhinitis is well established.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups: Clarinex is the proprietary name for desloratadine (established name). Clarinex is the metabolite of Claritin, which is a relatively non-sedating antihistamine.

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Clarinex is proposed for treatment of SAR and PAR at a dose of 5 mg once a day for patients 12 years of age and older.

- B. State of Armamentarium for Indication(s):** There are a number of antihistamines available for the treatment of allergic conditions, including perennial and seasonal allergic rhinitis. There are only two antihistamines approved for these conditions that are relatively non-sedating, i.e. Claritin (loratadine) and Allegra (fexofenadine). Zyrtec (cetirizine), which has been approved recently has a higher incidence of sedation than Claritin or Allegra. Intranasal corticosteroids are also first line treatment for allergic rhinitis. Avoidance measures and allergen immunotherapy are also important therapeutic modalities for the management of allergic rhinitis.
 - C. Important Milestones in Product Development:** see Section IA above.
 - D. Other Relevant Information:** none.
 - E. Important Issues with Pharmacologically Related Agents:** see above.
- II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews:** There were no Chemistry or Pharmacology issues relating to this NDA. This is the same formulation that was approved for use at the same dosage in patients with SAR (see Chemistry and Pharmacology Reviews).
- III. Human Pharmacokinetics and Pharmacodynamics**

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- A. Pharmacokinetics: There were 5 PK studies performed by the sponsor (see Biopharm Review).**
- 1. Study 1378 was an open, parallel, placebo-controlled, repetitive dose study over 5 weeks evaluating the concomitant administration of desloratadine with fluoxetine (Prozac) in 54 patients 22-49 years of age, of whom 49 were Caucasian. There was an 18% increase in the bioavailability of desloratadine when given concomitantly with fluoxetine. There was a 17% decrease and an 18% increase in the bioavailability of fluoxetine and norfluoxetine, respectively, when given concomitantly with desloratadine. There was no significant change in the QTc interval but a 4.7 bpm increase in ventricular rate was seen in patients who received these medications concomitantly.**
 - 2. Study 1380 was an open, crossover, single dose study evaluating the effect of grapefruit juice and food on the pharmacokinetics of desloratadine in 23 healthy adults, of whom 19 were Hispanic and 2 were slow metabolizers. The Cmax and AUC were essentially unchanged by either grapefruit juice or food.**
 - 3. Study 1381 was a third party blind, placebo-controlled, repetitive dose study where 90 healthy patients 19-46 years of age, of whom 89% were Caucasian, received desloratadine and azithromycin concomitantly. The concomitant administration of these medications resulted in up to a 19% increase in the bioavailability of desloratadine and a 31% increase in the bioavailability of azithromycin.**
 - 4. Study 1430 was discontinued when all 37 patients in the study developed adverse events after the concomitant administration of desloratadine and cimetidine in a sequestered setting. A number of patients developed palpitations, but no ECG changes were noted. All except one of these patients was Hispanic.**
 - 5. Study 1866 was performed because study 1430 was discontinued and was identical to that study. It was an open, parallel, repetitive dose study where 36 healthy patients 22-45 years of age, of whom 94% were Caucasian, received desloratadine and cimetidine concomitantly. No slow**

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metabolizers were identified. There was up to 10% increase in the bioavailability of desloratadine with the concomitant administration of these two drugs.

- B. Pharmacodynamics: No significant adverse events or significant changes in ECG parameters were noted after the concomitant administration of ketoconazole, erythromycin, azithromycin, cimetidine or fluoxetine.**

IV. Description of Clinical Data and Sources

- A. Overall Data: In NDA 21,165 for Clarinex in the treatment of SAR, 4 multicenter, double-blind, placebo-controlled, randomized, parallel, repetitive dose studies of 2-4 weeks duration in patients 12 years of age and older with SAR were submitted. Studies 223, 224, and 225 compared desloratadine at daily doses of 5 and 7.5 mg with placebo in adult and adolescent patients with SAR. A total of 487 patients received 5 mg of desloratadine, while 489 patients received 7.5 mg of desloratadine in these studies. The primary efficacy variable in these studies was change from baseline in average reflective 12 hour AM/PM total symptom score over the first 2 weeks of treatment. Total symptom score included four nasal symptoms (rhinorrhea, nasal congestion, nasal itching and sneezing) and five non-nasal symptoms (itchy eyes, tearing, eye redness, itching of the ears and palate and cough). In the fourth study (study 001), 173 patients received doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg and 20 mg over a period of 2 weeks. This study had the same primary efficacy variable as the other 3 studies. In addition, in NDA 21,165, the sponsor provided data on 4 single dose onset of action studies, studies in patients with renal and hepatic impairment, patients concomitantly receiving erythromycin and ketoconazole, and pharmacokinetic studies in specific ethnic groups, in comparison with loratadine and after food ingestion. Also, cardiac effect was assessed in one study in which patients received 45 mg per day of desloratadine for 10 days.**

In regard to the three studies comparing response to 5 mg and 7.5 mg per day of desloratadine, efficacy was demonstrated with 7.5

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mg but not 5 mg in one study, 5 mg but not 7.5 mg in one study and with both doses in the third study. In addition, the efficacy of the 5 mg per day and higher doses was demonstrated in study 001. Therefore, 2 of the 4 repetitive dose studies submitted in NDA 21,165 demonstrated the efficacy of desloratadine at a dose of 5 mg daily. The safety of desloratadine at a dose of 5 mg per day was demonstrated in all the studies. In the high dose study (45 mg per day for 10 days), there was a 4 msec greater prolongation of the QTc interval than placebo based on machine reading of the QTc interval and maximum QTc interval from serial ECGs. Interaction studies with concomitant administration of desloratadine and erythromycin and ketoconazole did not show any adverse cardiac effect.

The sponsor has submitted 2 studies evaluating patients with PAR; studies 218 and 219 (see Appendix for details of these studies). One of these studies, study 218 demonstrated the efficacy of desloratadine for the treatment of nasal symptoms of PAR, based on statistical significance of difference from placebo. The efficacy of desloratadine was not demonstrated for nasal congestion or for non-nasal symptoms, such as the ocular symptoms that frequently accompany allergic rhinitis. Study 219, on the other hand., failed to show efficacy for desloratadine in the treatment of PAR, based on the primary efficacy variable or any other objective assessment. The safety of desloratadine was demonstrated in both studies.

The sponsor has also submitted 2 studies that evaluate the effectiveness and safety of Clarinex in the treatment of SAR in patients who also have asthma (studies 214 and 215). In study 214, a dose of 5 mg of desloratadine was significantly more efficacious than placebo in reducing symptoms of SAR. When analyzed from both a reflective and point-in-time standpoint. Significant improvement was seen as early as the first day of treatment for total symptoms, nasal symptoms, non-nasal symptoms and all individual symptoms except for nasal congestion. The effectiveness of this dose of desloratadine was demonstrated over the entire treatment interval based on scores at the end of the dosing interval that were significantly lower than were seen after

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placebo administration. A dose of 5 mg of desloratadine produced mixed results in terms of its effect on the lower respiratory tract. There was not a significant effect on pulmonary function, in particular FEV-1, although a significantly greater improvement was seen in the desloratadine group in terms of total asthma symptoms, wheezing, cough and beta agonist use. These data are consistent with other data in the literature that demonstrate an effect of antihistamines on lower respiratory symptoms without an effect on pulmonary function. In contrast, while the efficacy and safety of desloratadine for the treatment of nasal symptoms associated with SAR was demonstrated in study 215, there was no efficacy demonstrated for ocular symptoms, which are often associated with SAR. Although there was some indication of an effect of desloratadine on lower respiratory symptoms, objective assessments did not demonstrate any efficacy of desloratadine in the treatment of asthma.

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B. Tables Listing the Clinical Trials: See table below of studies done with 5 mg of Clarinex.

Study #Clinical pharmacology	Study objective	Study design	Treatment arms	Number of pts
1380	grapefruit juice effect of	Single dose, crossover	Clarinex 5 mg	24
1378	Concomitant administration fluoxetine	Single dose and repetitive dose., parallel	Clarinex 5 mg fluoxetine 20 mg placebo	54
1381	Comcomitant administration azithromycin	Repetitive dose parallel placebo -controlled	Clarinex 5 mg Allegra 60 mg Zithromax 250	90
1430	Concom admin with cimetidine	Repetitive dose parallel	Clarinex 5 mg cimetid 300 mg	37
868	Comcomitant administration with cimetidine	Repetitive dose parallel	Clarinex 5 mg Cimetidine 300 mg	36
PAR, study #	Study objective	Study design	Treatment arms	Number of pts
218	Efficacy/safety	Double-blind parallel, 4 week repetitive dose	Clarinex 5 mg per day, placebo	676
219	Efficacy/safety	Double-blind parallel, 4 week repetitive dose	Clarinex 5 mg per day, placebo	698
SAR, study #	Study objective	Study design	Treatment arms	Number of pts
001	Dose-ranging efficacy/safety	Double-blind parallel 2 week repetitive dose	Clarinex 2.5, 5, 7.5, 10, 20 mg daily, placebo	1036
223	Efficacy/safety	Double-blind parallel 2 week repetitive dose	Clarinex 5 and 7.5 mg per day placebo	496
224	Efficacy/safety	Double-blind parallel 2 week repetitive dose	Clarinex 5 mg and 7.5 mg per day, placebo	492
225	Efficacy/safety	Double-blind parallel 4 week repetitive dose	Clarinex 5 mg and 7.5 mg per day, placebo	475
SAR/asthma	Study objective	Study design	Treatment arms	Number of pts
214	Efficacy/safety	Double-blind parallel 4 week repetitive dose	Clarinex 5 mg montelukast 10 mg/day, placebo	501
215	Efficacy/safety	Double-blind parallel 4 week repetitive dose	Clarinex 5 mg montelukast 10 mg	423

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- C. Postmarketing Experience: Based on spontaneous adverse event reports, there were no safety concerns raised.**
- D. Literature Review: A literature review was done by the Sponsor and reviewed. Conclusions on the efficacy and safety of desloratadine, based on the studies submitted in the NDA were not changed by this data.**

V. Clinical Review Methods:

- A. How the Review was Conducted: The summarized data submitted by the sponsor in the NDA was reviewed in detail and supported when necessary by individual patient data. No review of the literature was necessary for this NDA. Assessment of the NDA was initiated with a review of the data submitted under the original NDA for SAR. The four new placebo-controlled, double-blind, repetitive dose studies submitted by the sponsor were the first part of the NDA reviewed. The pharmacokinetic data submitted by the sponsor was then reviewed and the total database evaluated in regard to the proposed labeling.**
- B. Overview of Materials Consulted in Review: The data submitted with this NDA for use of Clarinex in patients with PAR and with concomitant asthma in conjunction with a review of the data submitted with the original NDA for use of Clarinex in patients with SAR served as the database.**
- C. Overview of Methods Used to Evaluate Data Quality and Integrity: There was no reason, based on a review of the data submitted to doubt the quality or integrity of the database for this drug product in this patient population.**
- D. Were Trials Conducted in Accordance with Accepted Ethical Standards: There were no ethical issues associated with this NDA.**
- E. Evaluation of Financial Disclosure: '**

It was concluded that the centers represented by these investigators did not affect the conclusions reached on the efficacy and safety of this drug product.

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VI. Integrated Review of Efficacy

- A. Brief Statement of Conclusions:** The data from study 218 demonstrate the efficacy of Clarinex in the treatment of PAR and the data from studies 214 and 215 demonstrate, in conjunction with the studies submitted in NDA 21,165, the efficacy of Clarinex in the treatment of SAR. The efficacy of Clarinex in the treatment of asthma was not consistently demonstrated in studies 214 and 215.
- B. General Approach to Review of the Efficacy of the Drug:** The efficacy of Clarinex in the treatment of SAR was reviewed based on the data submitted in NDA 21,165, in conjunction with the data provided for studies 214 and 215 in this NDA. The efficacy of Clarinex in the treatment of PAR was reviewed in studies 218 and 219, with the understanding that the underlying pathophysiology is basically the same in SAR and PAR and the effect of Clarinex on these two conditions would not be expected to be different. The efficacy of Clarinex in the treatment of asthma was evaluated in studies 214 and 215. In each of these studies, a table was developed to summarize the parameters that were used to evaluate efficacy, e.g. AM/PM reflective point-in-time and reflective assessment of the total symptom score. Based on whether the primary outcome variable showed a statistically significant difference from placebo and was supported by secondary parameters, a determination of the efficacy of Clarinex was determined for each study. A determination was then made based on all the studies done in regard to the efficacy of Clarinex for PAR and asthma.
- C. Detailed Review of Trials by Indication:** A detailed review of the studies performed by the sponsor can be found in the Appendix.
- D. Efficacy Conclusions:** Based on the data provided in this NDA, supported by the data provided previously in NDA 21,165, the sponsor has demonstrated the efficacy of Clarinex for both SAR and PAR. The sponsor has not provided sufficient data to support any claim for the efficacy of Clarinex in the treatment of asthma.

VII. Integrated Review of Safety

- A. Brief Statement of Conclusions:** The data from studies 214, 215, 218 and 219 demonstrate the safety of Clarinex for the treatment of SAR and PAR in patients 12 years of age and older. In addition, review of the integrated summary of safety, the 4 month safety update and spontaneous adverse drug event reporting support the safety of Clarinex for the treatment of PAR and SAR.

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- B. Description of Patient Exposure:** There were 1655 patients who received Clarinex for the treatment of allergic rhinitis, 66% of whom were female, and 79% of whom were Caucasian. Treatment for 3-4 weeks was given in approximately 65% of these patients, for at least 2 weeks in approximately 90%.
- C. Methods and Specific Findings of Safety Review:** Each study submitted by the sponsor was reviewed independently in regard to safety parameters, which included adverse events, vital signs, laboratory tests, and ECGs. In addition, the Integrated Summary of Safety and the 4 month safety update submitted by the sponsor were reviewed in regard to each of the se safety parameters. In addition, the pharmacokinetic/pharmacodynamic studies submitted by the sponsor were reviewed, assessing, in particular, any changes in ECG parameters, especially QTc interval after administration of Clarinex when given concomitantly with other medications. The details of the safety review can be found in the Appendix (Also see review by Biopharm). There were no safety issues raised by review of this data that would preclude approval of this drug product. Patients have been exposed to desloratadine as the metabolite of loratadine in a clinical setting since the approval of loratadine without any signal from post-marketing surveillance of any safety issue.
- D. Adequacy of Safety Testing:** The methods used to assess safety were adequate to define safety in adult and adolescent patients with PAR and SAR.
- E. Summary of Critical Safety Findings and Limitations of Data :** see above and Appendix, especially in terms of the need for labeling changes.
- VIII. Dosing, Regimen, and Administration Issues:** The proposed dose of Clarinex for the treatment of PAR is the same as that already approved for the treatment of SAR, i.e. 5 mg tablet once daily. This is an appropriate dose for SAR and PAR.

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IX. Use in Special Populations: There was no significant variation in the efficacy or safety of Clarinex in the studies submitted, based on race, gender, or age. Slow metabolizers of desloratadine have been demonstrated, with a higher incidence of this finding in African-American patients, where 20% are slow metabolizers.

- A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation:** The sponsor's evaluation and analysis of gender effects is acceptable.
- B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy:** The sponsor's evaluation for the effect of age, race and ethnicity is acceptable.

C.

- D. Comments on Data Available or Needed in Other Populations:** The sponsor was asked to attempt to determine the mechanism responsible for higher levels of drug exposure in some patients (slow metabolizers of desloratadine) and to assess the potential for drug-drug interaction that might be expected pending the outcome of these investigations. The basis for this request is the finding that there is a substantial subset of patients who have a significantly higher exposure to desloratadine than most patients, based on AUC. The exposure to desloratadine resulting from repetitive administration in such patients is estimated to be 6-9 times greater than the exposure in adult patients as a whole. Furthermore, there are no data to identify the mechanism for the higher levels in these patients and no means of prospectively identifying those patients who might have greater exposure. If these patients are inherently slow metabolizers of desloratadine, then the number of patients who experience high exposure in clinical use may be much greater, particularly if there is a deficient metabolic pathway that may be inhibited by concomitant medications.

X. Conclusions and Recommendations

- A. Conclusions:** The data submitted by the sponsor support the efficacy and safety of Clarinex in the treatment of PAR in patients 12 years of age and older.

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- B. Recommendations:** Clarinex, in the tablet form, is approvable for the treatment of symptoms of PAR in patients 12 years of age and older.

XI. Appendix

- A. Other Relevant Materials:**

1. Labeling:

- a. Description Section:** acceptable as written
- b. Clinical Pharmacology Section:** In the Pharmacokinetics: Absorption: section, the sponsor states that "Neither food nor grapefruit juice had an effect on the bioavailability...of desloratadine." This statement is supported by study 1380. Table 1 should be reheaded.

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- c. Clinical Trials Section:** The statement regarding the number of patients who received Clarinex is accurate.

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and should be deleted.

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- d. Indications and Usage Section: The sponsor has demonstrated that Clarinex tablets are safe and effective for the relief of nasal and non-nasal symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older.**
- e. Adverse Reactions Section: the changes made in this section, which reflect the increased database from the 4 new studies performed with a dose of 5 mg per day, are acceptable.**
- f. Overdosage Section: The sponsor's changes are acceptable.**

B. Individual More Detailed Study Reviews

1. Studies evaluating Clarinex for PAR:

**a. Study 218: 33 centers; 21 centers in the US
Number of patients: 676; 337 in the DCL group and 339 in the placebo group; 337 patients in each group for the ITT analysis; 296 patients in the DCL group and 298 patients in the placebo group were included in the efficacy analysis**

Age range: 11-79 years

Patient population: PAR, moderate, at least a two year history; IgE-mediated response to appropriate perennial allergen

Study design: multicenter (USA, Canada, Germany), randomized, placebo-controlled, double-blind, parallel study

Drug administration: 5 mg of desloratadine

Periods of study: 4 weeks of randomized treatment following up to a 14 day screening period; Evaluation was performed on day 1, day 8, day 15 and day 29

Parameters evaluated: the primary efficacy variable was the mean change from baseline in AM/PM point-in-time TSS (excluding nasal

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congestion) average over the 4 weeks of treatment; secondary efficacy variables included total symptom score with nasal congestion, total nasal symptom score with and without nasal congestion, total non-nasal symptom score, individual symptom scores, overall patient condition and response to therapy. Patients assesses symptoms twice daily. Nasal symptoms included rhinorrhea, PND, nasal congestion, nasal itching, and sneezing. Non-nasal symptoms included ocular symptoms and itching of the ears/palate. Efficacy variables were evaluated in terms of reflective scoring as well as point-in-time scoring. Safety variables included AEs, VS, lab tests, and ECGs. ITT and efficacy-evaluable datasets were analyzed

Study results:

Efficacy: Two data sets were analyzed: all randomized patients (intent-to-treat [ITT]) and an efficacy-evaluable subset (EES) of patients defined as all randomized patients who met key eligibility and evaluability criteria. There were 337 patients evaluated at baseline but only 325 on day 1 due to unperformed evaluations at the only evaluation time point on day 1, i.e. PM evaluation.

There were 41 patients excluded from the efficacy-evaluable subset. Most patients were between the ages of 18 and 65 years (91% of the patients who received desloratadine) and the majority were female (68% of the desloratadine patients) and Caucasian (82% of the desloratadine patients). A similar demographic pattern was seen in the patients who received placebo (v39, p59).

The primary efficacy outcome variable was the average change from baseline in AM/PM instantaneous (point-in-time, NOW) total symptom score (TSS), excluding nasal congestion, over 4 weeks of treatment (days 1-29) compared with placebo (v39; p60). There was a statistically significantly greater mean improvement from baseline based on evaluation of the ITT population (as well as the EES) in the group that received desloratadine compared to the group that received placebo at all time points except day 1 ($p = 0.06$), i.e. on days 2, 3, and 4 and for the periods of days 1-8, 9-15, 16-22, 23-29 and 1-29 (v39; p61) in regard to the primary outcome variable. The difference in the mean improvement in the desloratadine and placebo groups

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was not, in this reviewer's opinion, clinically significant. There were 11 patients in the desloratadine group without data on day 1, which was only the PM value because they did not diary data at this first time point.

The amount of improvement in NOW AM/PM TSS was greater in women (38%) than in men (28%) after receiving desloratadine. There was also a slightly greater degree of mean improvement in women who received placebo. There was a greater mean percent change in Caucasians and in patients < 65 years of age, although any interpretation of this data is difficult because of relatively small number of patients who were non-Caucasian (N =122) and the very small number of patients 65 years of age and older (N =13)(v39 p152-158). Of the centers with more than 3 patients, more efficacy was shown in the group that received desloratadine at 16 centers compared to 12 centers where placebo was more efficacious.

Reflective TSS and TNSS excluding nasal congestion also demonstrated a statistically significant difference between the desloratadine and placebo groups at all time points except for the last week of the study (v39;p64). Total NOW nasal symptom score, excluding nasal congestion also demonstrated a statistically significant difference between desloratadine and placebo at all time points except for day 1 (v39; p 65).

In terms of TNNSS NOW, only on day 3 and for the period of days 1-8 was there a statistically significant difference between the group that received desloratadine and the group that received placebo (v39; p68). In contrast, there was a statistically greater improvement in the group that received desloratadine when TNNSS was evaluated reflectively at all time points except for the last week of treatment (v39; p69).

In terms of mean AM/PM NOW and reflective individual symptom scores over days 1-29, desloratadine was more effective than placebo, based on statistical significance for rhinorrhea, sneezing and post-nasal drainage (PND). Desloratadine was effective for itching of the nose, when assessed by NOW evaluation but not by reflective evaluation. Desloratadine was not effective for nasal congestion,

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itching, burning or watering of the eyes or itching of the ears or palate, either on NOW evaluation or reflective evaluation (v39; p70). There was a good deal of variation, however. For example, in regard to PND, based on AM/PM NOW evaluation, there was a statistically significantly greater mean improvement in the desloratadine group at all time points (v39; p 209). In contrast, based on AM/PM reflective evaluation, there was a statistically significant difference only on days 1, 2, and 4, as well as days 1-8 and days 1-29 (v39; p228), a similar pattern to that seen when PND was assessed based on AM NOW evaluation (v39; p247). Interestingly, when patients were asked to reflect in the morning about the previous 12 hours, efficacy on a statistical basis, was demonstrated for rhinorrhea, PND and itching of the ears/palate (v39; p260-267). On the other hand, when asked to assess symptoms at a given time in the evening, efficacy on a statistical basis was demonstrated for rhinorrhea, nasal itching, sneezing, PND and itching of the ears/palate (v39; p279-286). Overall condition and therapeutic response were assessed jointly by the patient and the investigator. In terms of overall condition, there was no difference between desloratadine and placebo (v39;p72). In terms of therapeutic response, the percentage of patients who had a moderate, marked or complete relief was essentially the same in the two treatment groups. This does not support a statistically significant difference between the two treatment groups in regard to this parameter (v39;p73, p313)

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Mean change from baseline based on ITT population

Parameter change	DCL change from baseline p value	placebo change from baseline	DCL change from baseline	percent
TSS AM/PM NOW * days 1-29	- 3.7	- 3.0	35.0%	0.005
TSS AM/PM NOW # days 1-29	- 4.1	- 3.3	33.1%	0.01
TSS AM/PM reflect * days 1-29	- 4.2	- 3.4	37.9%	0.007
TSS AM/PM reflect # days 1-29	- 4.5	- 3.8	36.0%	0.01
TSS AM NOW * days 1-29	- 3.5	- 2.8	32.7%	0.02
TSS AM NOW # days 1-29	- 3.8	- 3.1	31%	0.04
TSS AM reflective * days 1-29	- 3.9	- 3.2	37%	0.01
TSS AM reflective # days 1-29	- 4.3	- 3.6	35%	0.02
TSS PM NOW * days 1-29	- 4.0	- 3.1	36%	0.002
TSS PM NOW # days 1-29	- 4.4	- 3.4	34%	0.005
TSS PM reflective * days 1-29	- 4.4	- 3.6	38%	0.008
TSS PM reflective # days 1-29	- 4.8	- 4.0	37%	0.01
TNSS AM/PM NOW * days 1-29	- 2.3	- 1.7	33%	0.001
TNSS AM/PM NOW # days 1-29	- 2.6	- 2.0	31%	0.006
TNSS AM/PM reflective * days 1- 29	- 2.5	- 2.1	36%	0.007
TNSS AM/PM reflective # days 1-29	- 2.9	- 2.4	33%	0.02
TNSS AM NOW * days 1-29	- 2.1	- 1.6	31%	0.005
TNSS AM NOW # days 1-29	- 2.4	- 1.9	29%	0.02
TNSS AM reflective * days 1-29	- 2.4	- 2.0	35%	0.02
TNSS AM reflective # days 1-29	- 2.7	- 2.3	32%	0.05
TNSS PM NOW * days 1-29	- 2.4	- 1.8	34%	< 0.001
TNSS PM NOW # days 1-29	- 2.8	- 2.2	32%	0.005
TNSS PM reflective * days 1-29	- 2.7	- 2.2	36%	0.005

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Mean change from baseline based on ITT population (continued)

	DCL Change from baseline	placebo change from baseline	DCL percent change	p value
TNSS PM reflective # days 1-29	- 3.1	- 2.6	34%	0.009
TNNSS AM/PM NOW days 1-29	- 1.5	- 1.2	36%	0.08
TNNSS AM/PM reflective days 1-29	- 1.6	- 1.3	40%	0.02
TNNSS AM NOW days 1-29	- 1.4	- 1.2	34%	0.26
TNNSS AM reflective days 1-29	- 1.6	- 1.3	39%	0.02
TNNSS PM NOW days 1-29	- 1.6	- 1.3	39%	0.03
TNNSS PM reflective days 1-29	- 1.7	- 1.4	40%	0.05
Rhinorrhea AM/PM NOW days 2-29	- 0.55	- 0.40	26%	0.003
Nasal congestion AM/PM NOW days 2-29	- 0.32	- 0.32	16%	0.91
Nasal itching AM/PM NOW days 2-29	- 0.58	- 0.46	37%	0.01
Sneezing AM/PM NOW days 2-29	- 0.60	- 0.46	38%	0.005
Itching/burning eyes AM/PM NOW days 2-29	- 0.52	- 0.45	35%	0.14
Tearing eyes AM/PM NOW days 2-29	- 0.47	- 0.40	35%	0.14
PND AM/PM NOW days 2-29	- 0.53	- 0.39	25%	0.009
Itching ears/palate AM/PM NOW days 2-29	- 0.47	- 0.40	39%	0.12
Overall condition	- 0.58	- 0.54	25%	0.52
Therapeutic response	3.41	3.54	-----	< 0.001

* excluding nasal congestion

including nasal congestion

TSS = total symptom score

TNSS = total nasal symptom score

TNNSS = total non-nasal symptom score

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Conclusions: The efficacy of desloratadine for the treatment of nasal symptoms of PAR, based on statistical significance of difference from placebo, has been demonstrated in this study. However, in this reviewer's opinion, the improvement seen after administration of desloratadine, when compared with the improvement seen after administration of placebo was not clinically significant. The efficacy of desloratadine was not demonstrated for nasal congestion or for non-nasal symptoms, such as the ocular symptoms that frequently accompany allergic rhinitis.

Safety:

Adverse events: In regard to adverse events that occurred with a frequency of 2% or more, pharyngitis was reported in 3% of patients who received desloratadine compared with 1.5% of patients who received placebo. Two patients developed palpitations while receiving desloratadine not requiring interruption of treatment. More women in both the desloratadine and the placebo groups developed adverse events, 29 and 36%, respectively, than did men, 19% and 20%, respectively. The incidence of treatment-related adverse events was essentially the same in the two treatment groups. Severe adverse events were not significantly different in the two treatment groups. There was no significant difference between the number of patients who discontinued because of adverse events in the desloratadine and placebo groups (v39; p77-87). A 44 year old Caucasian female was discontinued from the study because of elevated liver function tests. There were 4 serious adverse events, 3 in patients who received desloratadine, none of which was considered to be related to the study drug (v39; p88). Somnolence occurred in 3 patients (1.1%) in the desloratadine group and 2 patients (0.7%) in the placebo group.

Laboratory tests: No clinically significant changes in median lab values were noted. Based on the degree of change in laboratory values, no clinically relevant patterns were noted. There were no differences in laboratory tests based on age, gender or race. Lab tests were considered to be clinically relevant if a blood chemistry value was 2.6 times or more the upper limit of the normal reference range, hemoglobin was 9.4 g/dL or less, the platelet count was

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74,000/uL or less, or the WBC was 2900/uL or less. A 47 year old Hispanic male who received desloratadine had an SGPT of 37 U/L, an SGOT of 23 U/L, an alkaline phosphatase of 93 U/L, a BUN of 4.9 mmol/L and a creatinine of 88 umol/l at baseline. After treatment with desloratadine his SGPT rose to 131 U/L (NRR = 0-45), his SGOT rose to 72 U/L (n = 15-45), his alkaline phosphatase rose to 408 U/L (NRR = 30-115), his BUN rose to 14.9 and his creatinine rose to 539 umol/L (NRR = 53-133) (V40, p526-527). It is not clear if this change in liver and renal function tests was due to desloratadine.

One patient who received placebo had an increase in SGPT from 84 U/L at baseline to 140 U/L after treatment (v39; p92).

Vital signs: Increases from baseline in systolic and diastolic blood pressure of 30% or more were more common in the group that received placebo than in the group that received desloratadine. There were a higher percentage of patients in the desloratadine group than in the placebo group who had an increase in heart rate of 30% or more, but the difference was not clinically significant.

ECGs: All QTc intervals were recalculated using the Fridericia and the Bazett correction because different center formulas were used to calculate intervals from computerized tracing machines. Change in ventricular rate was 2.1 bpm in the desloratadine group and 1 bpm in the placebo group. There was a decrease in the QTc interval using the Fridericia correction of 0.9 msec in the desloratadine group (v39; p96). There were no patients who received desloratadine and had a 15% or greater prolongation of the QTc interval (Fridericia correction) (v39; p98)

Conclusions: There are no safety issues related to the administration of desloratadine based on the data provided for this study, desloratadine is safe for administration to patients with PAR.

b. Study 219: 30 centers in the US and other countries

Number of patients: 698; 348 received DCL; 350 received placebo; 346 patients who received DCL and 349 patients who received placebo were included in the ITT analysis, while 310 patients in the

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DCL group and 328 patients in the placebo group were included in the efficacy analysis.

Age range: 12-80 years

Patient population: PAR; at least 2 year history of moderate symptoms

Study design: double-blind, placebo-controlled, multicenter, parallel, randomized study

Drug administration: 5 mg once daily

Periods of study: randomized treatment for 4 weeks

Parameters evaluated: primary efficacy variable was mean change from baseline in AM/PM point-in-time TSS excluding nasal congestion averaged over the 4 weeks of treatment; secondary efficacy variable included TSS with nasal congestion, total nasal symptom score with and without nasal congestion, total non-nasal and individual symptom scores, overall patient condition and response to therapy; both point-in-time and reflective evaluations were done by patients; safety parameters included AEs, VS, lab tests, and ECGs.

Study results:

Efficacy:

Two data sets were analyzed: An intent-to-treat (ITT) population and an efficacy-evaluable subset (EES). The latter population was composed of all randomized patients who met key eligibility and evaluability criteria. There were 38 patients in the desloratadine group and 22 patients in the placebo group who were not included in the EES of patients (v44, p57-68).

Most patients (85-88%) were 18-64 years of age, female (63-70%) and Caucasian (76-77%). There were 47 patients (14%) in the desloratadine group and 33 patients (9%) in the placebo group who